REMARKS

Claims 5-13 and 18-21, directed to non-elected subject matter, have been cancelled without prejudice or disclaimer to the filing of one or more divisional applications directed thereto.

Claim 1 has been amended to precisely recite that in the organism-compatible material with combined extracellular matrices of the present invention in which a calcification layer is formed on a base, the extracellular matrices are combined with the base through the medium of the calcification layer.

New claims 22 and 23 have been added to the aplication. New claim 22 recites that the base of the organism-compatible material with combined extracellular matrices of the invention is a material which allows the formation of a calcification layer thereon, the formation taking place because the base absorbs phosphoric acid. Claim 23 recites that the calcification layer combines directly with the base. New claim 22 is supported in the specification by the description on page 12, lines 25-29, and the description on page 11, lines 10-14. New claim 23 is supported by the description of the invention in the four corners of the specification and in the drawings.

Reconsideration and removal of the 35 U.S.C. § 102 rejection of the claims of the application as being anticipated by the material produced in Example 6 of Ashkar et al. (U.S. Patent No. 6,509,026) ("Ashkar") or by the matrix coated substrates produced by the method disclosed in Van Blitterswijk et al. (U.S. Patent No. 6,152,964) ("Van Blitterswijk") are respectfully requested.

The organism-compatible material of this application and the materials for organisms of Ashkar and Van Blitterswijk have the common point that each of the materials comprises a base material, a layer formed on the base material, and an extracellular matrix formed on the layer. However, as described below, the material of the layer attached to the base in the organism-compatible material of the present invention is distinct from the material attached to the base of the materials of Ashkar and Van Blitterswijk. Additionally, the layer attached to the base in the organism-compatible material of the present invention is combined with the base material more firmly than the layers of Ashkar and Van Blitterswijk are combined with the base materials.

Accordingly to the present invention, a calcification layer such as hydroxyapatite is formed on a base material, and various

types of cells can be cultured on the calcification layer to form various types of extracellular matrices on the layer. Thus, the present invention provides organism-compatible materials with extracellular matrices whose origins are various types of cells.

On the other hand, according to the invention of Ashkar, a layer of osteopontin is formed on a base material. Therefore, the cells which can be cultured on the osteopontin layer are limited to osteoblasts. According to the invention of Van Blitterswijk, a layer of undifferentiated cells is formed on a base material. Specifically, a base material is put in a culture solution to allow substances in the solution to stick to the base material. It is not verified whether the substances sticking to the base material are an extracellular matrix or not. If they are an extracellular matrix, the extracellular matrix is young and weak, unlike the mature extracellular matrices according to the invention of the invention of the present application.

According to the invention of the present application, the calcification layer is formed on the base material and is combined with the base material firmly at the molecular level. The calcification layer is firmly combined with the base material.

Then, an extracellular matrix is formed on the calcification layer and combined firmly with the calcification layer as a matter of course. Therefore, when the organism-compatible material with the combined extracellular matrix is applied to a region of an organism, the extracellular matrix does not come off the calcification layer and the calcification layer does not come off the base material. On the other hand, the osteopontin layers of Ashkar merely stick to the base materials. Therefore, if extracellular matrices are combined firmly with the osteopontin layers, the osteopontin layers and the extracellular matrices on them are liable to come off the base materials when the materials for organisms are applied to regions of organisms. The undifferentiated cells of Van Blitterswijk merely stick to the base materials. Therefore, the strength of combining the cells with the base materials is small.

It is noted that the calcification layer formed on a base material in the present invention is a layer which is formed on a material with "calcification activity", i.e., a material which absorbs phosphoric acid onto its surface. The "apatite film" shown in the attached document titled "Quasi-biological apatite film

induced by titanium in a simulated body fluid" by Li and Ducheyne, *Wiley* (1998), and the "surface film" shown in the attached document titled "Characterization of surface film formed on titanium in electrolyte using XPS" by Hanawa and Ota, *Applied Surface Science* (1992), are calcification layers.

The calcification layer is composed of calcium, phosphoric acid, and carbonic acid. Osteopontin is a protein and, therefore, is different from a calcification layer. "Undifferentiated cells" are simply cells and, therefore, are also different from a calcification layer.

According to the inventions of Ashkar and Van Blitterswijk, matrices are calcified, but neither the osteopontin layer nor the layer of undifferentiated cells is a calcification layer. Although there is no difference between the culture conditions to form a calcification layer on a base material according to the invention of the present application and the culture conditions to calcify matrices according to the inventions of Ashkar and Van Blitterswijk, the location where calcification takes place according to the invention of the present application is different from the locations where calcification takes place according to the

inventions of Ashkar and Van Blitterswijk. A calcification layer is formed on the surface of a base material according to the present invention, whereas a top matrix layer is "mineralized" according to the inventions of Ashkar and Van Blitterswijk. Besides, as noted previously, the surface of a base material is covered with osteopontin or undifferentiated cells according to the inventions of Ashkar and Van Blitterswijk. Therefore, a calcification layer is not formed on the surface of a base material. In this regard, Example 6 of Ashkar is merely a comparison of the mineralization of HOS cells on different base materials and does not suggest formation of a calcification layer on a base material.

Finally, neither Ashkar nor Van Blitterswijk discloses the use of any base material which absorbs phosphoric acid to form a calcification layer on its surface.

Thus, it can be seen that neither Ashkar nor Van Blitterswijk discloses an organism-compatible material with combined extracellular matrices which includes each of the elements of the organism-compatible material with combined extracellular matrices recited in the claims of the present application. Removal

of the 35 U.S.C. § 102 rejections is believed to be in order and is respectfully solicited.

The foregoing is believed to be a complete and proper response to the Office Action dated April 4, 2003, and is believed to place this application in condition for allowance. If, however, minor issues remain that can be resolved by means of a telephone interview, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number indicated below.

In the event that this paper is not considered to be timely filed, applicants hereby petition for an appropriate extension of time. The fee for any such extension may be charged to our Deposit Account No. 111833.

In the event any additional fees are required, please also charge our Deposit Account No. 111833.

Respectfully submitted,

KUBOVCIK & KUBOVCIK

Ronald J. Kubovcik
Reg. No. 25,401

Attachments: "Quasi-biological apatite film induced by titanium

in a simulated body fluid" by Li and Ducheyne, *Wiley* (1998)
"Characterization of surface film formed on titanium in electrolyte using XPS" by Hanawa and Ota, *Applied Surface Science* (1992)

Atty. Case No. YMA-002
The Farragut Building
Suite 710
900 17th Street, N.W.
Washington, D.C. 20006
Tel: (202) 887-9023
Fax: (202) 887-9093
RJK/cfm